

## ■ SHORT COMMUNICATION ■

# PULMONARY EMBOLISM DUE TO PROTEIN S DEFICIENCY IN PREGNANCY

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## SUMMARY

**Objective:** Inherited thrombophilia is an uncommon disease that may cause recurrent thrombosis and may complicate pregnancy. A patient with protein S deficiency suffered antepartum deep venous thrombosis (DVT) and antepartum pulmonary embolism (PE) in the following pregnancy. She had both successful pregnancies managed by anticoagulant and close fetal surveillance.

**Case Report:** A 28-year-old woman with protein S deficiency experienced an episode of DVT of the left lower extremity in her first pregnancy and an episode of PE in her second pregnancy. In both pregnancies, the venous thromboembolism (VTE) was treated successfully with low-molecular-weight heparin (LMWH).

**Conclusion:** Prophylactic anticoagulant therapy should be administered throughout the antepartum and postpartum periods for pregnant women with inherited thrombophilia and a previously documented VTE. LMWH is the first-line drug of choice for both prophylaxis and treatment of VTE since it does not cross the placenta and is not teratogenic. [*Taiwanese J Obstet Gynecol* 2005;44(3):294–296]

**Key Words:** deep venous thrombosis, heparin, pregnancy, protein S deficiency, pulmonary embolism, venous thromboembolism, warfarin

## Introduction

Although thromboembolism is uncommon during pregnancy and the postpartum period, obstetricians should be alert to the possibility because the complications, such as pulmonary embolism (PE), are often life-threatening. The estimated incidence of pregnancy-associated venous thromboembolism (VTE) varies from 1 in 1,000 to 1 in 2,000 deliveries [1]. PE occurs in approximately 16% of patients with untreated deep venous thrombosis (DVT) and remains the major cause of maternal death in Western countries [2]. Hereditary protein S deficiency is estimated to be associated with about a tenfold increase in the risk of the first episode of VTE in Caucasians [3]. Pregnancy is also a risk factor for VTE in women with inherited thrombophilia. The

antepartum risk of VTE is thought to be 4% for carriers of protein S deficiencies [4]. We present a case of protein S deficiency diagnosed during pregnancy. The patient experienced an episode of DVT of the left lower extremity in her first pregnancy and an episode of PE in her second pregnancy. We also discuss the prophylaxis and treatment of VTE.

## Case Report

A 28-year-old woman was referred to our hospital in her first pregnancy at 9 weeks of gestation due to progressive painful swelling of the left leg for 2 days. Vascular duplex examination revealed DVT from the mid-femoral region to above the knee in the left lower extremity. Her free protein S level was 107% (normal, 44–115%) and her functional protein S level was 36% (normal, 53–144%). Other coagulation data such as antithrombin III (AT III), protein C, lupus anticoagulant, and anticardiolipin antibody were within normal limits. Protein S deficiency was diagnosed. Low-molecular-weight heparin (LMWH) was administered (fraxiparine 3,800 IU/0.4 mL twice daily). She was discharged on the 16<sup>th</sup> day when the

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symptoms subsided, but received LMWH until delivery. She had a normal spontaneous vaginal delivery at 38 weeks of gestation without complications. Postpartum LMWH was continued for 2 months during the breast-feeding period. Subsequently, despite taking warfarin for 1.5 years, vascular duplex examination showed partial thrombi in her left lower extremity.

The patient's second pregnancy began 0.5 months after warfarin was discontinued. At 6 weeks of gestation, her free protein S level was 49% and her functional protein S level was 45%. Prophylactic anticoagulant was not given because of her stable condition. Unfortunately, she was sent to our emergency department due to dyspnea and aggravated left upper chest sharp pain at 11 weeks of gestation. At that time, D-dimer was 6.94  $\mu\text{g/mL}$  (normal,  $< 0.5 \mu\text{g/mL}$ ) and chest magnetic resonance imaging revealed filling defects in bilateral pulmonary arteries. Wedge-shaped high-intensity lesions were noted in the superior segment of the left lower lobe and left lingular segment. These findings were compatible with PE. Her dyspnea and chest pain improved gradually after LMWH therapy (clexane 60 mg/0.6 mL twice daily). She tolerated room air well and her D-dimer level dropped to 0.87  $\mu\text{g/mL}$  within 6 days. She received long-term LMWH until term normal spontaneous vaginal delivery and during postpartum breast-feeding. The delivery and postpartum courses were smooth.

## Discussion

Protein S is a cofactor for the inactivation of factors Va and VIIa by activated protein C [5]. It may also inhibit a number of coagulation factors independently of protein C. Protein S synthesis is vitamin K-dependent and occurs in the liver. One-third of protein S circulates in a free form and two-thirds is present as a complex with complement 4b-binding protein [5]. Only the free form is active.

Virchow postulated three main causes of thrombosis: stasis of the blood, changes in the composition of the blood, and changes in the vessel wall [6]. All three of these conditions can occur in pregnancy and during puerperium. Therefore, hypercoagulability and compression of the venous system by the gravid uterus are the major causes of VTE in pregnancy. Prophylactic anticoagulant should be given in hemophilic pregnant women [7].

Anticoagulant regimens for pregnancy include warfarin, unfractionated heparin (UFH) and LMWH. Warfarin is a coumarin derivative that inhibits the action of vitamin K. However, oral warfarin is contraindicated in the first trimester because it crosses the placenta and

is teratogenic; its teratogenic effect is less during the second and third trimesters. Warfarin can also cause maternal and fetal bleeding and spontaneous fetal loss [8]. Fetal intracranial hemorrhage is a possible severe complication during the third trimester. Heparin can be substituted from 6 to 12 weeks to eliminate embryopathy, but activated partial thromboplastin time (aPTT) should be monitored closely. Although limited data indicate that warfarin cannot be detected in breast milk, there is some uncertainty about its use in women who are breast-feeding.

Heparin is the drug of choice for both prophylaxis and treatment of VTE. However, the side effects of long-term use of heparin in pregnant women include osteoporosis, thrombocytopenia, and an increased risk of bleeding. UFH acts primarily by binding to AT III. The resulting heparin-AT III complex inactivates several coagulation enzymes [9]. Heparin dosage should be adjusted to achieve an aPTT that is 1.5–2.5 times the control value. If a therapeutic aPTT level cannot be reached, an anti-Xa level (plasma heparin) of 0.3–0.7 U/mL 6 hours after the dose, equivalent to a heparin level of 0.2–0.4 U/mL by protamine titration, should be used [10].

LMWH acts primarily by exerting an anti-Xa effect. It has a longer plasma half-life than UFH and provides a more predictable dose response, which allows once- or twice-daily administration. LMWH is also associated with a lower risk of maternal osteopenia and thrombocytopenia than UFH [9]. These advantages over UFH make LMWH the agent of choice for preventing and treating VTE in pregnant women [11]. Since women gain weight during pregnancy, the dosage of LMWH should be adjusted. Bates and Ginsberg suggest three dosing options [12]. First, the initial dose can be maintained throughout pregnancy. Second, the dose can be adjusted to account for weight gained over the pregnancy. Third, heparin (anti-Xa) levels can be measured 4–6 hours after the morning dose on a periodic basis.

In this case, protein S deficiency was diagnosed during the episode of DVT at 9 weeks of gestation in the patient's first pregnancy. Her symptoms subsided after LMWH treatment. An episode of PE occurred in her second pregnancy at 11 weeks of gestation. Management with LMWH was also successful. Women with hereditary hypercoagulable states such as AT III or protein C and S deficiencies and a previous episode of VTE are expected to be at a higher risk of acute VTE during pregnancy than asymptomatic carriers with these abnormalities. Therefore, prophylactic anticoagulant therapy should be given throughout the antepartum and postpartum period. The newer LMWHs are the best choice because

they can be administered once or twice daily, have a predictable dose response, and do not require constant monitoring. However, the cost of these agents may somewhat limit their use. Long-term use of UFH or LMWH can lead to osteoporosis, thrombocytopenia, and an increased risk of bleeding. Oral warfarin can be substituted in the second trimester and the postpartum period. Warfarin should be used in patients with a mechanical valve prosthesis.

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